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Review Article

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How to Treat Metal Hypersensitive Alopecia Areata and Atopic Alopecia

Hideo Nakayama* and KoRon Chen

Abstract

Metal allergy was found with severe types of alopecia areata (AA) at the rate of 69.9% and the elimination of metal allergens from dental metals, cooking instruments lead to satisfactory hair regrowth and prevention of severe relapse of AA for the period of in average four years and four months at the rate of 75.5%. The cooperation of dentists for analysis of dental metals, removing allergic alloys and replacing to ceramics were needed. Another causation of AA was type I and IV allergy to house dust mite (HDM). This type has been called atopic alopecia historically. There is enough evidence that HDM is the main causation of atopic dermatitis (AD). Severe and intractable AD could be cured by the mite fauna investigation by methylene blue agar (MBA) method, followed by environmental improvement to decrease mites to less than 50/m^2 everywhere in the home. The same solution was applied to treat severe atopic alopecia cases, which were cured at the rate of 58.3%, and the longest record of confirmed period of cure was five years. When six years or more elapsed after the onset of AA, any kind of treatment was not successful, because biopsy of the scalp revealed the disappearance of hair follicles, which was replaced by dermal fibrosis. Therefore, the treatment of AA should start quickly, investigating allergy to metals and HDM.

Keywords

Alopecia areata; Metal allergy; Atopic alopecia; Atopic dermatitis; House dust mite (HDM)

Introduction

Alopecia areata (AA) is difficult to cure when it is a severe form such as the ones listed in Table 1. Histopathology of such cases show marked destruction of mostly the lower part of the hairfollicles, which are invaded by numerous lymphocytes which lead to massive hair loss (Figure 1). These lymphocytes are mainly CD4 positive T-cells, mingled with a smaller ratio of CD8 positive T-cells [1-7].

Temporal hair regrowth is possible with severe AA by systemic perorally administered predonisolone (PSL) [8,9] or intramusculary injected triamcinolone acetonide of 40-50 mg once a month [10,11]. These two facts are evidences that AA is an allergic disease.

There are always causative allergens when there are chronic allergic diseases. The discovery and exact elimination of the causative allergens are essential treatment to completely cure intractable chronic allergic diseases. It has been so with various allergic contact dermatitis [12], bronchial asthma, urticaria [13], drug eruption, lichen planus [14-16], pustulosis palmaris et plantaris [12], and atopic dermatitis [17].

The causative allergens that provoke AA had not been known in the previous century, however, since the new millenium, metal allergy has gradually been recognized [14] (Table 2), and it has been clarified that mite allergy is the most crucial causation of atopic dermatitis (AD) [17-19]. The term atopic alopecia had been described by several authors already from the 1960s [20,21], however, as acarology had not been studied by a number of dermatologists, the responsibility of house dust imtes (HDM) in producing AD had been unnoticed for many years till today.

This is a report that two important allergens, metal ions, and with other cases, HDM are recognized as the causes of severe AA, and their exact elimination will often lead to a long lasting cure of this intractable disease.

Metal Allergy Makes a Wide Spectrum of Allergic Dermatitis

The chracteristics of metal allergy

Metals (M) do not sensitize people, however, when metals lose the outermost electrons to form metal ions (M^{n+}, Figure 2), they do not already have the appearance of hard metals, rather they are water soluble haptens, which have strong affinity to human epidermal and hair follucle protein, ie keratin, at the sites of -SS-, -SH and -NH_2 (Figure 3) [14].

Keratin is our self component, therefore, it is not attacked by our own T-lymphocytes. Such self protection has been called immune privilege (IP) [22,23]. When metal ions meet keratin, either from outside of the body, or from inside of the body via blood streams when metal ions are taken from the mouth, then absorbed from the intestine, they produce complete antigen at the sites of keratin. Metal ions are elements, therefore, they are not destroyed either in the intestine or in the blood stream, and they act as haptens till they are expelled. Keratin is surely self, however keratin which conjugated metal ions are no longer self, in another word, an enemy substance to be attacked by one's own T-lymphocytes. Such an alteration is considered as the "collapse of IP [23]".

When metal ions come from the outside to the skins of those who are hypersensitive to M^{n+}, rejection reatction to M^{n+} keratin is exerted at the sites of contact in the form of erythema, edema, papules with severe itching. It is an allergic contact dermatitis and ancient

Table 1: Severe and intractable forms of Alopecia areata (AA).

1.	Alopecia universaris
2.	Alopecia totalis
3.	Alopecia diffusa
4.	Alopecia reticularis (alopecia areata multiplex confluens)
5.	Alopecia areata, which has present for over 6 years or more. (Cases in which the hair follicles almost lost from scalp has replaced by fibrosis.)

***Corresponding author:** Hideo Nakayama, Meguro Chen Dermatology Clinic, Shinyo-CK Building 6F 3-3-5, Kami-Ohsaki, Shinagawa-ku, Tokyo 141-0021, Japan, Tel: +81-3-3786-1678; Fax: +81-3-3786-1515; E-mail: nakayamadermatology@eos.ocn.ne.jp

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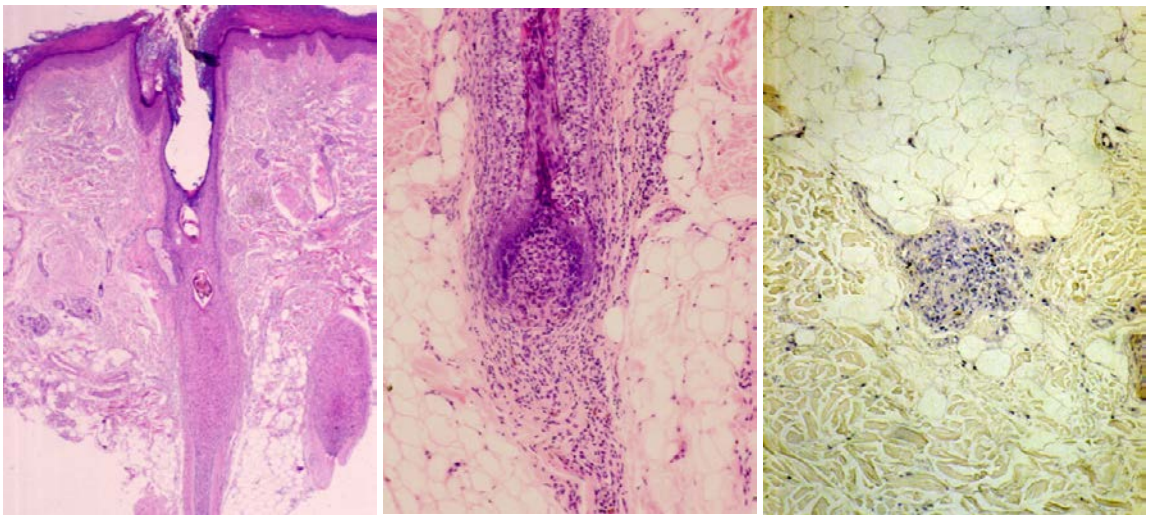
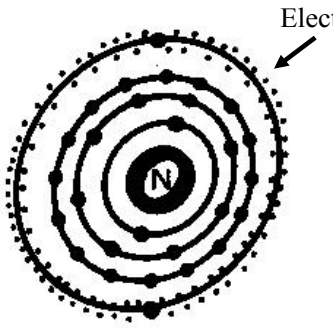


1a 1b 1c

Figure 1: Normal healthy hair follicle of the scalp showing straight and long hair sheath. Note that lymphocytic infiltration is not seen (1a). At the beginning of severe alopecia areata of the case of Figure 6. Note the massive invasion of lymphocytes destroying the hair follicle (1b). Such lymphocytes turned out to be CD4 positive T-lymphocytes (1c, case No.4 of Table 2).



Orbit	Number of electrons
K	2
L	8
M	18
N	32
O	32
P	10
Q	2
s	2
p	6
d	10
f	14

No. 28 Nickel (2 free electrons in the N orbit)

Effect of free electrons :

(1) Excellent transmission of electricity
(2) Flexibility
(3) Ionization to make M^{n+} (metal ions)

Figure 2: Structure of Atoms of Metals.

people called it "eczema". When metal ions come from inside, the diseases provoked by it are pustulosis palmaris et plantaris, eczema dyshidrosiforme [12,14], oral and/or cutaneous lichen planus [14-16,24-26] and generalized eczema including pseudo-atopic dermatitis (Shanon) [24]. Evidence of their causation is normally shown by a metal series patch test, or a challenge test involving the ingestion of $NiSO_4$ at 5 mg (as Ni^{2+}, 1 mg). But when this challenge test was performed at 30 mg (as Ni^{2+}, 6 mg) in one hospital, it provoked severe generalized dermatitis which had to be cured through hospitalization. Therefore, from ethical reasons, the challenge test should be done very carefully, only when it is indispensable to do so, in order to avoid medical claims.

Another characteristic of metal allergy is its unique cross hypersensitivity. For example, those who are sensitized to Ni^{2+}, often react to Co^{2+}, and those who are hypersensitive to Hg^{2+}, often react to Au^{3+} [25]. Nickel and cobalt, and also mercury and gold are quite different metals to each other, however when they become M^{n+}, by losing their outermost electrons, Ni^{2+} and Co^{2+} become very much alike, because the only difference of these two are the number of electrons at 3d in M orbit which is 7 and 8 respectively, and all other numbers and arrangement of electrons are the same after ionization of these two metals. That is why simultaneous positive reactions are often observed by patch testing with $NiSO_4$ and $CoCl_2$ [14].

Likewise, when a patient is sensitized by gold, often due to ear-piercing [25], the patch test reaction to $AuCl_3$ is naturally positive, and at the same time, the patient shows a positive reaction to $HgCl_2$.

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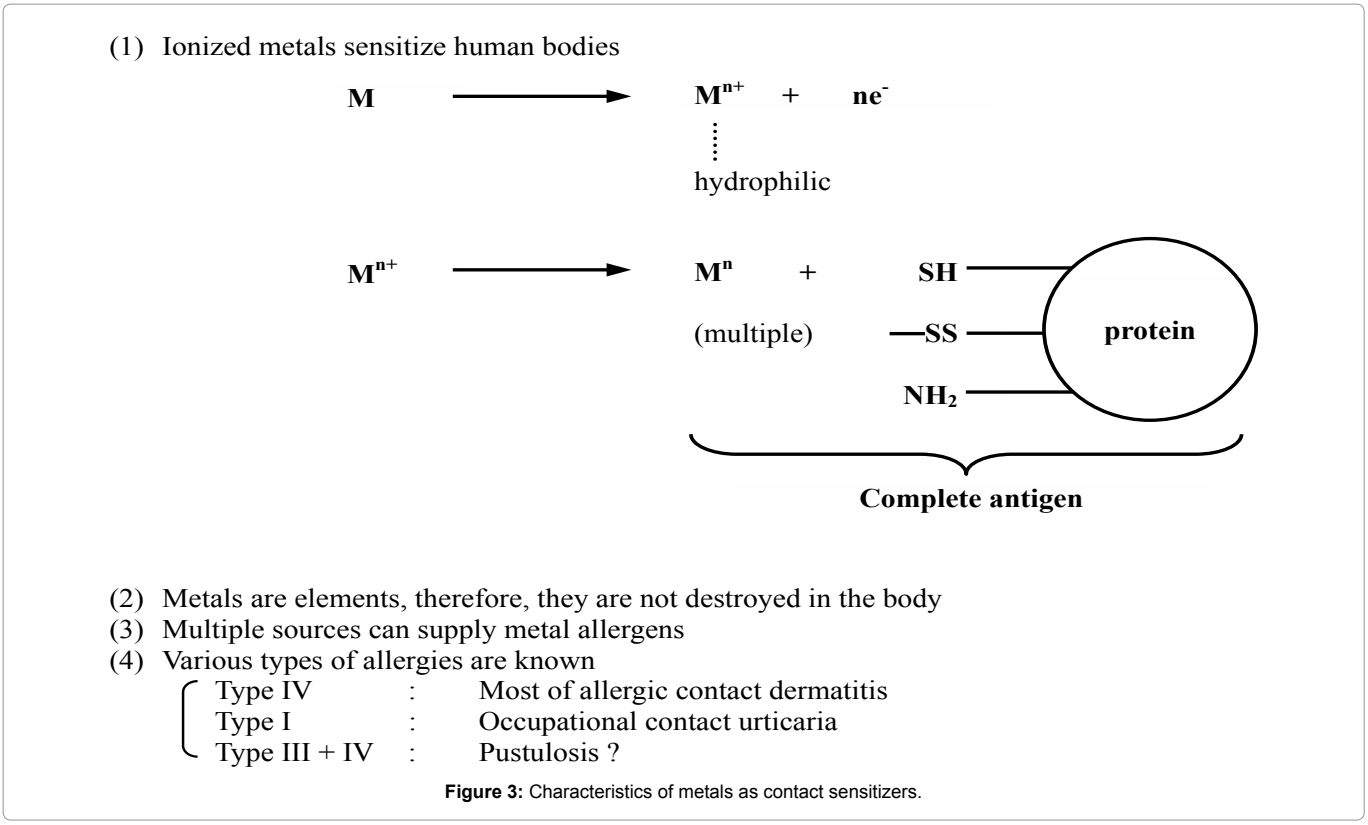


Figure 3: Characteristics of metals as contact sensitizers.

When ionized, the only difference between Au^{3+} and Hg^{2+} is that the numbers of electrons at 5d in 0 orbit are 8 and 10 respectively, while all other numbers and arrangements of electrons are completely the same [14]. This is why cross reactions occur frequently with Ni^{2+} and Co^{2+}, and also with Au^{3+} and Hg^{2+}. These cross reactions should be taken into consideration when causative metal allergens are to be eliminated for treatment for metal hypersensitive patients. The above mentioned cross reactions by the similarity of electron numbers and arrangements were previously reported [14].

When metal hypersensitiv alopecia areata was found

The discovery of the world's first case of severe alopecia areata due to metal allergy was almost coincidental. The case with its symptoms and the course of cure is demonstrated in Figure 4. This case suggested that systemically invaded Hg^{2+} was the causative allergen for her alopec

ia, because regrown hair was quickly lost by the innoculation of influenza containing mercury at 47.6 μg, and recurrent and intractable severe alopecia areata for the past four years was completely cured with no relapse by the elimination of all the dental HgAms and avoidance of inoculation.

The second case was a 24-year-old female suffering from alopecia diffusa for the past two months, which had been progressive and antisymptomatic treatment had been ineffective. Serum ANA and STS were negative, and serum IgE was in normal low range. Previously she suffered from allergic contact dermatitis due to metals, such as earring, necklaces etc. A patch test revealed that the contact allergen was nickel sulfate. In order to investigate the effect of systemically invaded Ni^{2+}, she consented to a challenge test of having perorally adminstered 1mg of $NiSO_4$ (0.2 mg as Ni^{2+}) for 5 days successively for a total of 5 mg of $NiSO_4$. Three days later, she revisited the hospital claiming that her defluvium of the scalp became progressive, and her area of alopecia had surely increased.

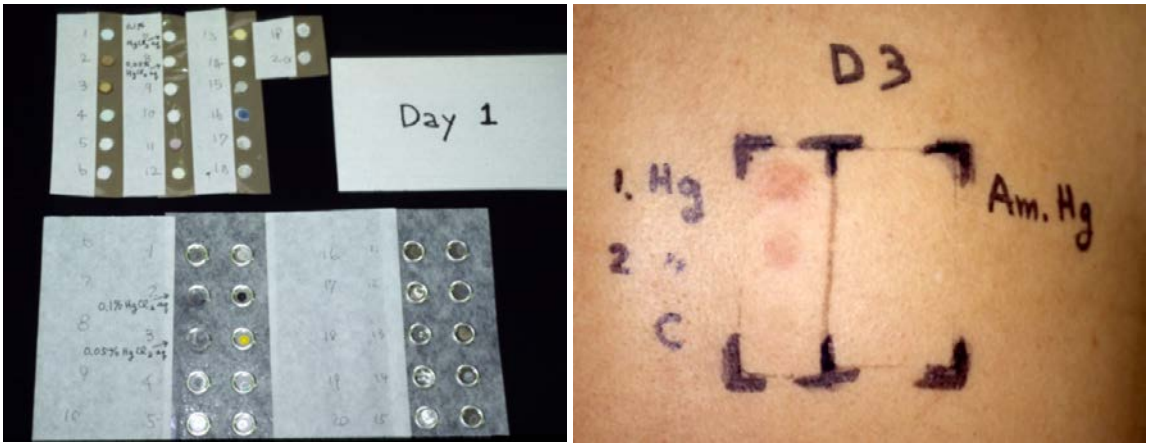
She was soon advised to stop the challenge test, and avoidance of Ni^{2+} started. As there had been no dental metals in the past, Ni^{2+} was considered to have come from the stainless steel pans and pots. Normally 18-8 stainless contained 18% chrome and 8% nickel. All of such pans and pots were requested to be changed to titanium or enamel coated pans and pots. After that the same antisymptomatic treatment composed of the application of herb lotions [2] brought almost cured conditions without any relapse.

From the third to eighth cases, they are listed in Table 2, and all of them were one by one reported in dermatological journals with photos in Japan and Europe (Croatia) [27-32].

Many cases followed

These initial cases strongly suggested the causation of metal ions on severe cases of alopecia areata. Therefore all the severe cases of alopecia areata were tested with a metal series patch test of M-9. Its results are demonstrated in Table 3, showing that the positive rates of every metal ions are very alike with alopecia areata (mild cases were excluded), contact dermatitis and atopic dermatitis. As metals are now common sensitizers in the world, the similarities of metal allergy in these three allergic diseases are understandable.

When metal allergy was clarified through a patch test, the positive cases to metal ions were examined to prove the multiple sources which had supplied metal ions to the patients. Table 4 shows the procedure, and dental metals were analysed by dentists capable of analysis using an electrone probe micro analyzer (EPMA) or X-ray fluorescence



4a 4b

Figure 4: Metal allergy is demonstrated by patch testing the metal series patch test allergens M-9 by using mainly water based metal salts on vinyl plasters (upper set). 0.1% $HgCl_2$ aq dissolves aluminum chambers (lower set) to produce false positive reactions (4a), therefore, this combination should be avoided. The usage of ammoniated mercury blocks the elution of Hg^{2+} ions to bring about false negative reactions (right row of 4b), while 0.1% and 0.05% $HgCl_2$ aq. on a vinyl plaster clearly produced positive reactions by confirmative patch test (left row of 4b) [27].

Table 2: Severe alopecia cases in which metal allergy are the likely causation (cases No.3 – 8).

S No.	Age & sex (F: female)	Onset of alopecia	Type of alopecia	Serum ANA	Serum IgE (IU/ml)	Patch test results	Result of metal analysis and electricity	Effect of removal of allergic metals	No. of Reference (Year)
3	37F	1.5 years	*A. universalis*	Titer 1:40 (+)	210	Ni(2+), Sn(2+)	Ni 85.9-9.9% in 6 dental metals	All 6 metals removed. Complete cure after one year.	28 (2001)
4	22F	2 years	*A. totalis*	negative	<170	Pd(2+), Pt(2+), Au(+)	All 6 dental metals contained Pd at 16.1-17.7% which were cathodes at 10-20 mV.	All 6 dental metals removed after which complete cure followed.	14 (2002)
								No relapse for the successive 3 years.	
5	30F	3 years	*A. universalis*	negative	250	Hg(2+), Au(2+)	3 HgAms were present.	All 3 Hg Ams removed.	29 (2004)
								Hair regrowth soon started, complete cure 6 month later.	
								For the next 9 months no relapse.	
6	48F	10 years (mild) 2 years (severe) (10 years previously dental metals were installed for the first time)	*A. diffusa*	negative	71	Pd(2+), Pt(2+)	All 6 dental alloys contained Pd at 15.3-40.2%	All 6 dental alloys removed.	30 (2006)
								Hair growth followed soon to complete cure at 6 months.	
								No relapse for the following 5 years.	
7	21F	10 months	*A. diffusa*	titer 1:40 (+)	530	Hg(2+)	9 out of 13 dental metals were HgAms,which contained Hg at 43.3 – 55.0%.	All 9 HgAms were eliminated to have brought complete cure.	31 (2012)
							They were cathodes at 130 – 80 mV.	No relapse for one year after the elimination.	
8	52F	More than three years	*A. universalis*	negative	294	Co(+); Sn(+)	4 dental metals contained stannic.	All 4 Sn containing metals were removed to bring complete cure.	31 (2012)
								No relapse was noted for 6 months after cure.	

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Table 3: Patch test results of the M-9 series. A comparison of positive rates with three dermatoses for 5 years (Years: 2011-2015).

Diseases				Alopecia areata (excluding mild cases)		Atopic dermatitis (AD)		Contact dermatitis	
				n	mean age	n	mean age	n	mean age
Male				27	36.4	71	36.7	71	46.3
Female				77	41.6	158	34.7	265	42.7
subtotal				104	40.3	229	35.3	336	43.5
No.	Metal salts	%	base	positive (number)	Positive rate (%)	positive (number)	Positive rate (%)	positive (number)	Positive rate (%)
1	$CuSO_4$	2	Aq.	9	8.7	28	12.3	33	9.8
2	$PdCl_2$	1	Aq.	8	7.7	8	3.5	33	9.8
3	$K_2Cr_2O_7$	0·4	Aq.	24	23.1	44	19.4	79	23.5
4	$NiSO_4$	5	Aq.	32	30.8	71	31.3	126	37.7
5	$NiSO_4$	2	Aq.	24	23.1	48	21.2	114	33.9
6	$CoCl_2$	2	Aq.	27	26.0	34	15.0	66	19.6
7	$HgCl_2$	0·1	Aq.	35	33.7	55	24.2	106	31.5
8	$HgCl_2$	0·05	Aq.	22	21.2	24	10.5	44	13.1
9	$SnCl_4$	1	Aq.	10	9.6	34	15.0	47	14.0
10	$CdSO_4$	1	Aq.	5	4.8	6	2.6	25	7.4
11	$HAuCl_4$	0·2	Aq.	8	7.7	10	4.4	36	10.7
12	H_2PtCl_6	0·5	Aq.	14	13.5	24	10.5	42	12.5
13	$FeCl_3$	2	Aq.	3	2.9	3	1.3	9	2.7
14	$InCl_3$	1	Aq.	2	1.9	8	3.5	14	4.2
15	$IrCl_4$	1	Aq.	3	2.9	2	0.9	3	0.9
16	$MoCl_5$	1	Aq.	5	4.8	27	11.9	28	8.3
17	AgBr	2	Pet.	0	0.0	0	0.0	2	0.6
18	$SbCl_3$	1	Pet.	0	0.0	1	0.4	0	0.0
19	$ZnCl_2$	2	Pet.	12	11.5	8	3.5	22	6.5
20	$MnCl_2$	2	Pet.	3	2.9	7	3.1	2	0.6

Note: (Aq.: Purified water, Pet.: Petrolatum)

Table 4: Recommended investigation and treatment when metal allergy is found.

1.	Perform a metal series patch test. The vehicle of NiSO4 and HgCl2 should be water on vinyl plaster with cloth or paper discs without using petrolatum, in order to avoid false negative reactions. The patch test should be performed for two days, and reactions should be read on the second, third (or fourth) and seventh (or sixth) days by ICDRG standards. (+) and (2+) are positive reactions.
2.	When metal allergens are found, check the metals in the oral cavity. If present, request an analysis of these metals to a dental clinic where a metal analysis by electron probe micro analyzer (EPMA) or X-ray diffraction method is available.
3.	The grade of electro-chemical dissolution of Mn+ in the oral cavity is measured by using an ammeter with two electrodes. The dissolution of Mn+ occurs at the dental metals as cathodes, in parallel with voltage and electric current (Faraday's law of electrolysis). Voltage and current is always parallel, therefore, only the measurement of voltage is necessary. When the mucous membrane is an anode with alloys cathode, Mn+ elutes from the cathode alloys. For example, HgAms are usually cathodes with a voltage of 100 - 200 mV to elute Hg2+ ions.
4.	After the evidence of metal allergy is obtained and the analysis data exhibiting the presence of the patch test's positive metals and their cross sensitizers is obtained, give the copy of these data to the patients, and explain that they suffer from metal allergy, and the causative metals are present in the oral cavity. When necessary, the electric current in the oral cavity is measured, and when cathode alloys contain metals to which the patients are hypersensitive towards, explain that the metal allergens elute from the dental alloys.
5.	Explain to them that the complete removal of dental metals to which the patients are hypersensitive towards could cure their severe alopecia areata and inform them that past records show a 70% chance of being able to maintain a cured condition. Notify them that with only antisymptomatic treatment, they may be only be cured temporarily and that there is a 50% chance of relapsing to their original conditions.
6.	Replace the metal pans and pots for cooking in the kitchen to non-metal pans and pots, such as ceramics, enamel-coated materials or strengthened glassware. Avoid having VB12 (cyanocobalamine) containing supplements, food and medication, when cobalt allergy is present.
7.	Start anti-symptomatic treatment till enough hair regrowth has been obtained, making sure that excess usage of corticosteroid is avoided. The use of herb lotions will help the treatment [2].
8.	High cacao chocolates should be avoided as it contains Cr, Co and Ni higher than other food.
9.	Inoculation of Hg / Thimerosal containing injectants should be avoided among Hg / Au hypersensitive patients.
10.	Follow up the patients after recovery for at least for two years.
11.	With those who are not allergic to any metal, the possibility of atopic alopecia or auto-immunity should also be considered.

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spectroscope (XRFS). All the causative metals with their cross reactors which showed positive reactions on a patch test were advised to be removed by the dentists. Substitutes were ceramics, titanium or the alloys of which components showed all negative reactions for the patients. Today a number of supplements and vitamins contain vitamin B_{12} (VB_{12}), or cyanocobalamine, and as Co^{2+} often cross reacts to Ni^{2+}, the ingestion of these cobalt containing supplements and vitamins were requested to be stopped.

The metallic pans and pots were also analysed when necessary, and they were also replaced by ceramics, enamel coated ones and hard glass-ware.

Anti-symptomatic treatment was given as before, and when hypermenstruation, peptic ulcers, diabetes mellitus, young ages, chronic infection and osteoporosis were present, the usage of systemic corticosteroid was refrained [2]. The discovery and elimination of causative allergens like Mn^{+} aimed to stop the relapse of severe alopecia for the recovered patients to go back to the previous miserable skin conditions. Therefore after complete or almost complete recovery was noted, they were followed up as long as possible. The statistics show that the rate of improvement by the elimination of causative metals from the oral cavity and cooking instruments was 75.5% (37 out of 49), and the cure was maintained in average for 4 years and 4 months. This is considered satisfactory because all these cases could not have been cured previously for 2 years or more, and the rate of relapse after a satisfactory recovery through antisymptomatic treatment only was considered as being more than 50% [11]. Such procedure to eliminate causative allergen to prevent relapse and consequently maintain cured condition was previously called "allergen control" [12]. The typical successful cases are demonstrated in Figures 5-9.

Treatment of atopic alopecia

The preliminary research performed in 1998 on 106 intractable alopecia areata confirmed the presence of atopic alopecia [3]. The rate of elevation of serum IgE at that time was 24.6% (16 out of 65 examined). When the severe alopecia areata patients showed negative patch test results to the M-9 series, and their serum IgE was high and xerotic eczema was noticed, they were considered as complicating atopic dermatitis (AD). Today the main causation of AD is considered as HDM allergy, as there is enough evidence for it shown in Table 5. Typical three cases of atopic alopecia who suffered from generalized eczema or prurigo Besnier for more than three years, hypersensitive to HDM, and cured by mite fauna examination, followed by environmental improvement to decrease mite number to less than 50/m^2 everywhere in the house are demonstrated in Figures 10 and 12. With these cases, cure after mite elimination has lasted for an average of 2 years. Considering that these cases could not have been cured previously, the fact that cure was maintained for more than 2 years should be recognized as valuable.

HDM antigens are composed of protein, fecal and enzymic allergen (P1), several terpens including a strong and primary sensitizer, α-acaridial (Figure 13). Protein is impossible to reach the lower half of the open hair follicle, however, the other two are considered to be absorbed into the open hair follicle canal, because they are soluble to sebum excreted from the adipose glands.

When mite elimination was performed for the case Figure 13 could regrow hair and the cured condition remained for 4 years. There were similar 14 (58.3%) out of 24 cases, with whom the treatment described in table 6 was recommended. Such allergen control has been successful with many cases of AD since 1995 [17],

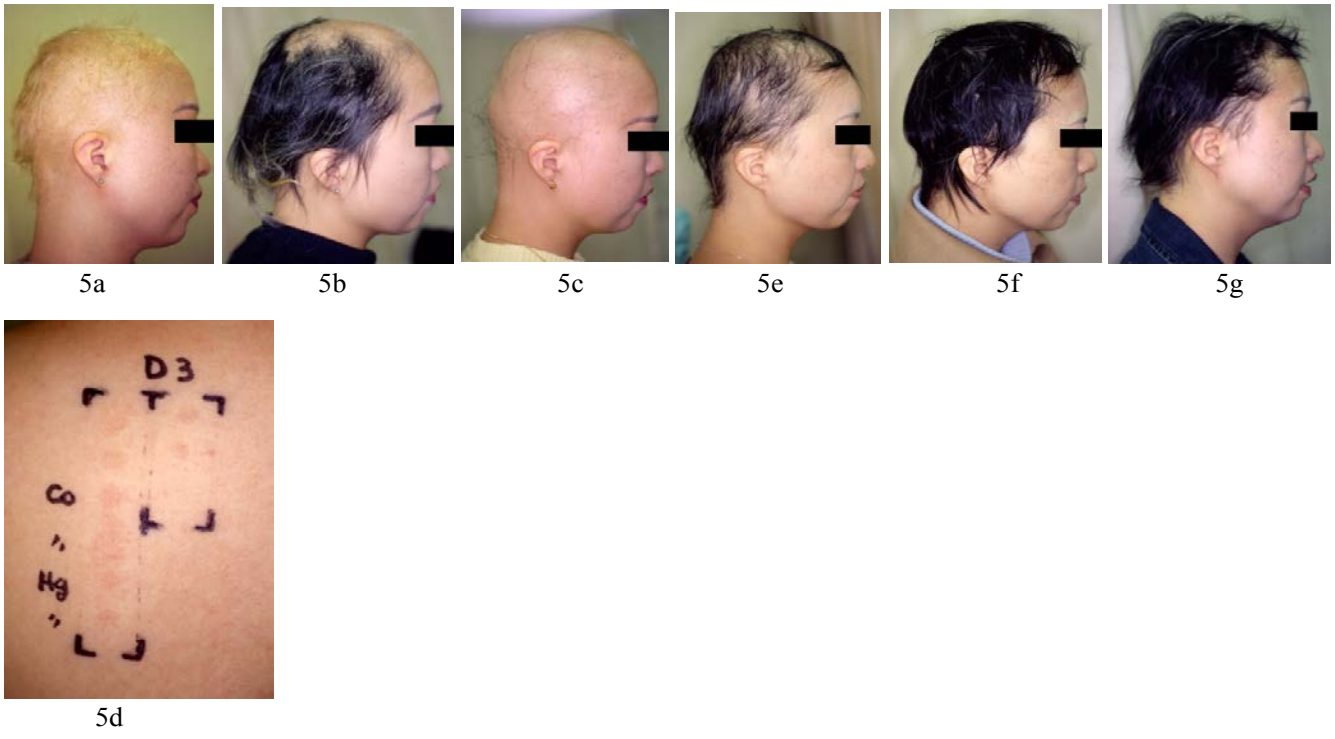

Figure 5: The world's first case of metal hypersensitive alopecia.

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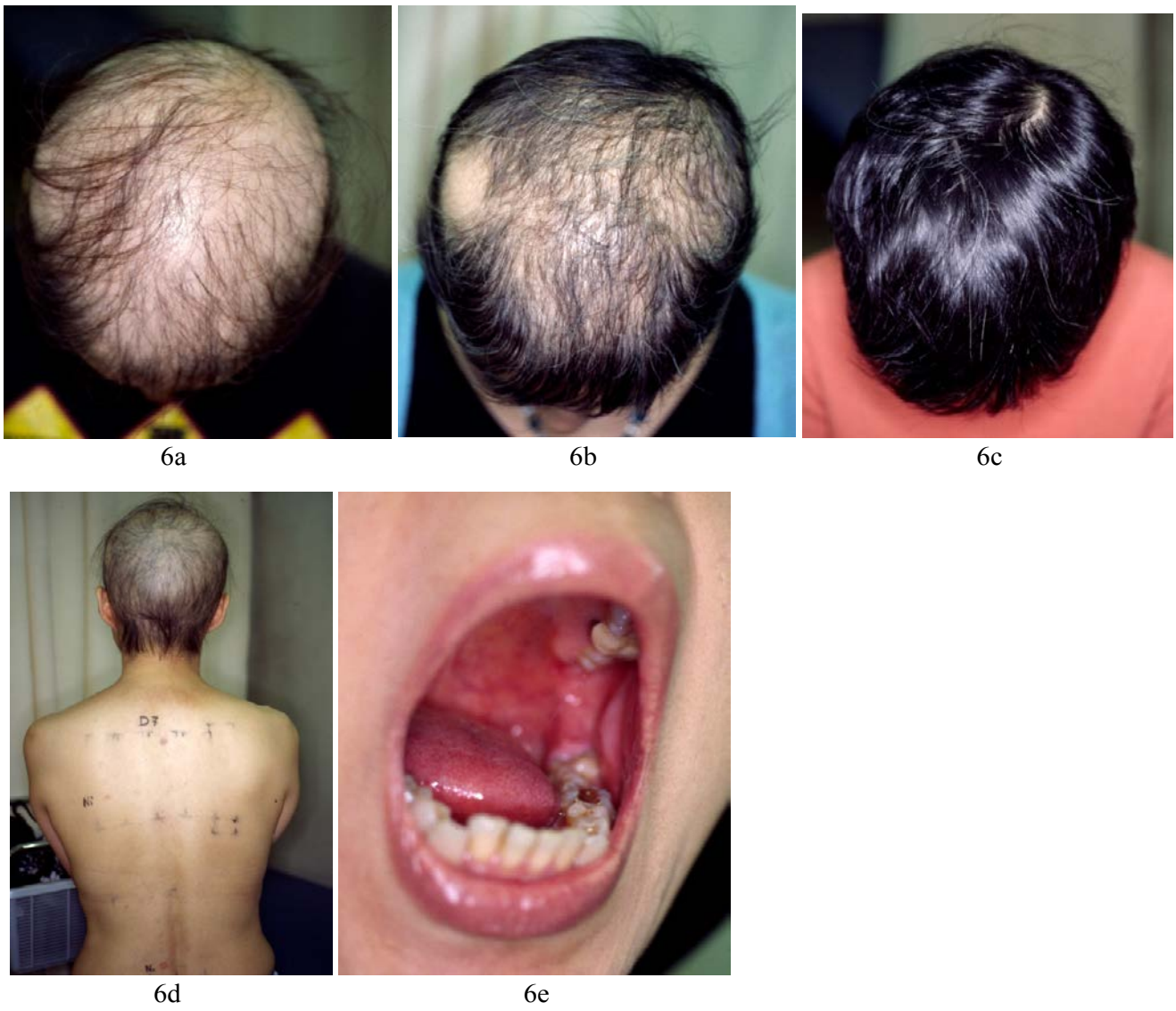

Figure 6: A case of metal hypersensitive alopecia due to dental metals.

Note: A 44-year-old female started having severe defluvium of the scalp, which progressed to develop into alopecia diffusa 4 months later (6a). As corticosteroid either perorally given or through six separate injection had been ineffective, she was patch tested using the M-9 series. $NiSO_4$ aq. at 5% was negative on days 2 and 3, however, became clear positive on day 7 of the patch test (6b). Serum ANA was negative, serum γ-globulin was elevated at 21·2%. Serum IgE was 435 IU/ml, however, RAST of 12 common sensitizers including HDM were all-negative. She had 3 dental metals in the oral cavity (6c), and their analysis demonstrated nickel at 0.1 – 1% level in one inlay and one metal bond. After their removal and exchange to ceramics, her hair quickly started to grow on the whole scalp (6d). 6 months later, her alopecia was almost cured (6e), and relapse has never been observed in 4 years of follow up.

but the similar experience on intractable atopic alopecia was the first report in 2017 [2].

Autoimmunity should be studied further

Before the hypersensitivity to metals and HDM was known, autoimmunity had been believed to be the main causation of severe cares of alopecia areata [5,6]. With a previous study on 106 cases of severe alopecia areata, serum ANA positive cases were 9 (31.0%) out of 29 cases studied [3]. At that time it was reported that among these 9 cases, 3 cases (10.3%) who showed ANA positive at 160 times serum dilution were considered to be due to autoimmunity, because the laboratory which examined ANA (SRL company, Tokyo) reported that with females 64 (10.5%) out of 593 controls who did not suffer from any autoimmune diseases showed ANA positive at 40 to 80 times dilution. Therefore, with alopecia areata cases, ANA positive at 40-80 times dilution does not mean autoimmunity, and if being ANA positive at 160-320 times serum dilution is a sign of autoimmunity, about 10% of severe alopecia areata should be considered as auto immunity.

An experimental animal model of alopecia was made using human alopecia skin transplanted to mice or rats, and the exserted

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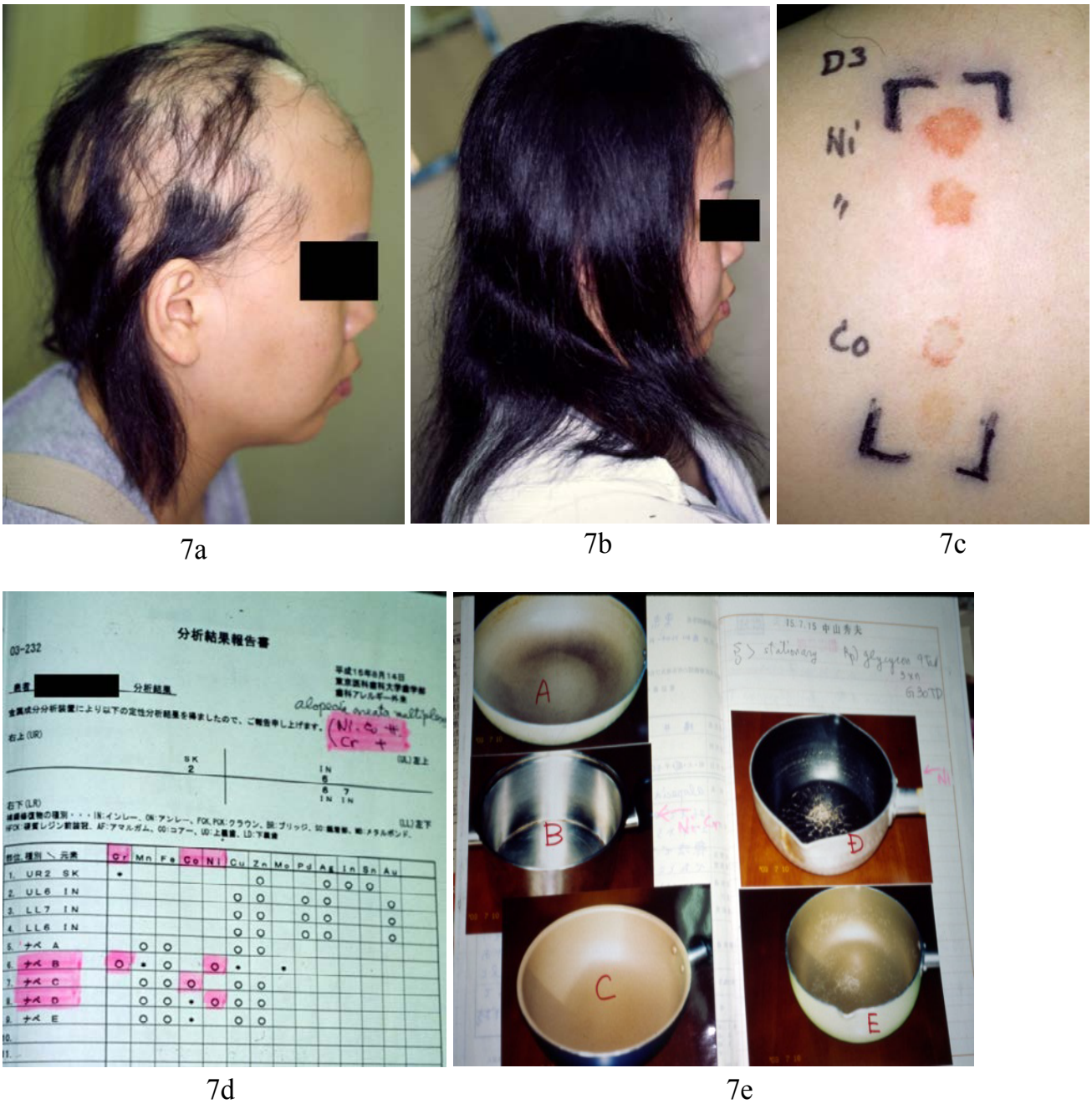

Figure 7: A case of metal hypersensitive alopecia areata due to pans and pots.

Note: A 28-year-old female had developed reticular alopecia areata a year and a half ago. The disease has been recurrent, and had not been cured successfully through any treatment (7a). A patch test showed that she was strongly sensitized to Ni and weak towards Co (7b). Serum ANA was positive at 40 times dilution, and this is considered as within normal female limit. Serum IgE was 840 IU/ml, however, RAST to HDM was not high, only Dp 14 UA to Df 6 UA. There were 9 dental metals, and analysis of dental metals showed that Ni and Co were not contained in them, rather 3 out of 5 metallic pans and pots used every day contained Ni and Co at more than 1% (7c). Scratch corrosion was seen on these pans and pots, suggesting the supply of metal allergens to the patient (7d). Subsequently, she was requested to dispose of all the metallic pans and pots, and the exclusive usage of ceramic pans and pots was requested. Predonisolne was stopped as she started showing signs of moon face. Trepan biopsy of the scalp and patch test positive reaction showed the dermal infiltration of lymphocytes with which CD4 positive cells were dominant to CD8 positive cells at both the skin lesion, suggesting that the same allergens have produced follicular destruction and spongiosis of the patch test. After the metallic pans and pots were disposed, her hair started to grow, and even though one small areata lesion has been present, the previous reticular multiple alopecia areata was cured completely, and the cure has been maintained for the following 8 years (7e).

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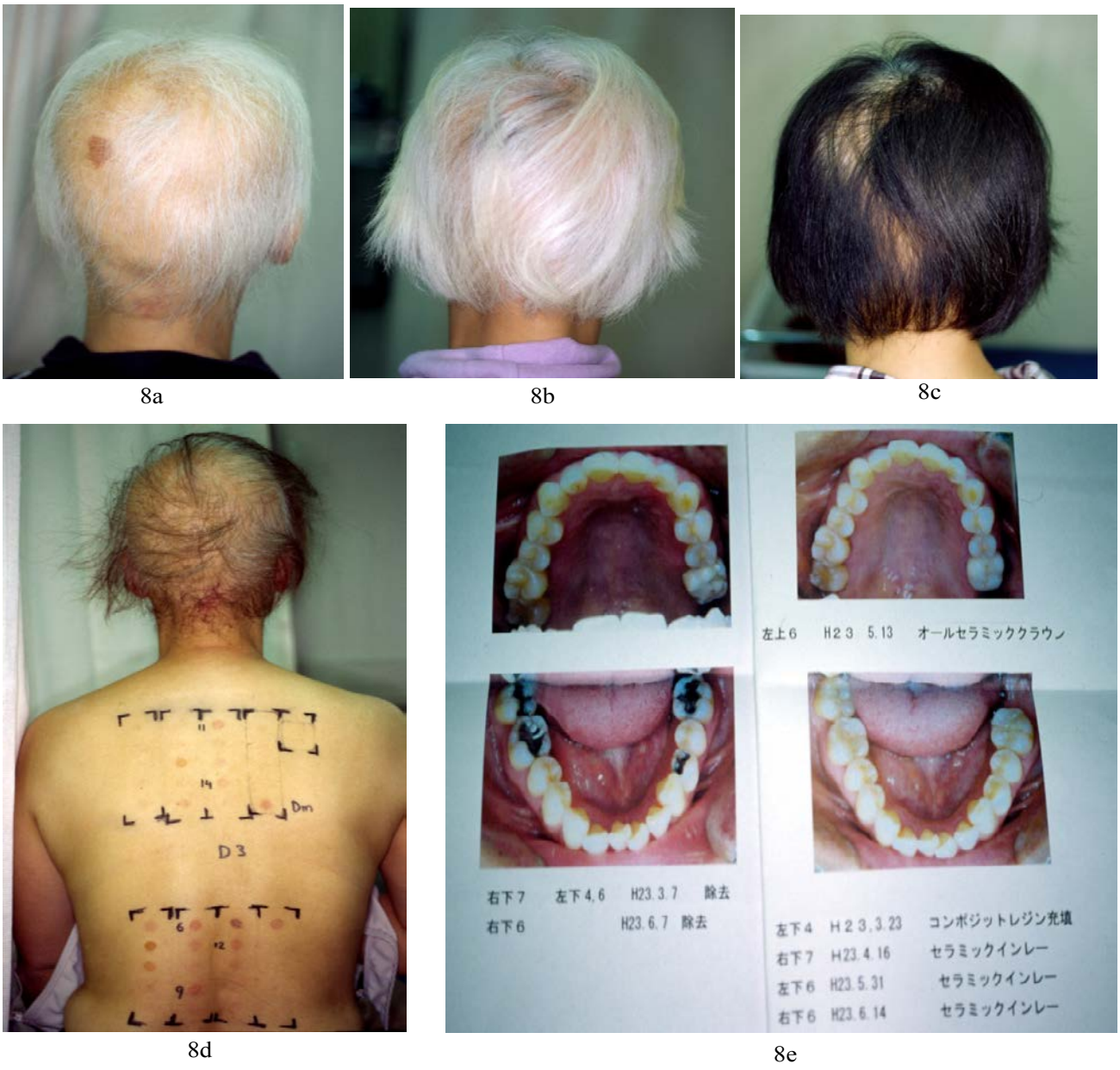

Figure 8: A case of metal hypersensitive alopecia areata.

Note: A 51-year-old woman suffered frequently from contact dermaitits due to her earrings. She had received dental treatment for 3 months, then massive defluvium happened for her to suffer from alopecia universalis (8a). ANA(-), CBC, liver function test results were normal. Serum IgE was 294 IU/ml. A patch test revealed that she showed clear positive reactions to stannic and cobalt (lower 6,9 of 8b). As there was no improvement by antisymptomaic treatment, four dental alloys in the oral cavity were analysed and showed that Sn was contained in them at 1.0 - 0.1%. The patient consented to eliminate all these alloys to be replaced by ceramics (8c. from left to right). After the alloys were removed, her hair regrew (8d), and cure was noted and continued more than 6 months of follow up (8e).

T-lymphocytes to have produced alopecia was CD8 (+) and NKG 2D positive T-lymphocytes, different from human alopecia which is caused by CD4 (+) and CD8 (+) T-lymphocytes. Human hairfollicle components are self to human, but non-self to mice or rats, therefore this type of experimental alopecia is not an auto-immune reaction. Using normal human hairfollicle components to find out what components produce autoimmune allergy was once planned, but not accepted to be performed in an university from ethycal reasons. Therefore this is still a problem to be investigated in the future.

Conclusions

Severe types of alopecia areata (AA) are difficult to cure, because even it has been known to be an allergic disease, yet the causative allergens have not been detected. Autoimmunity was most suspected

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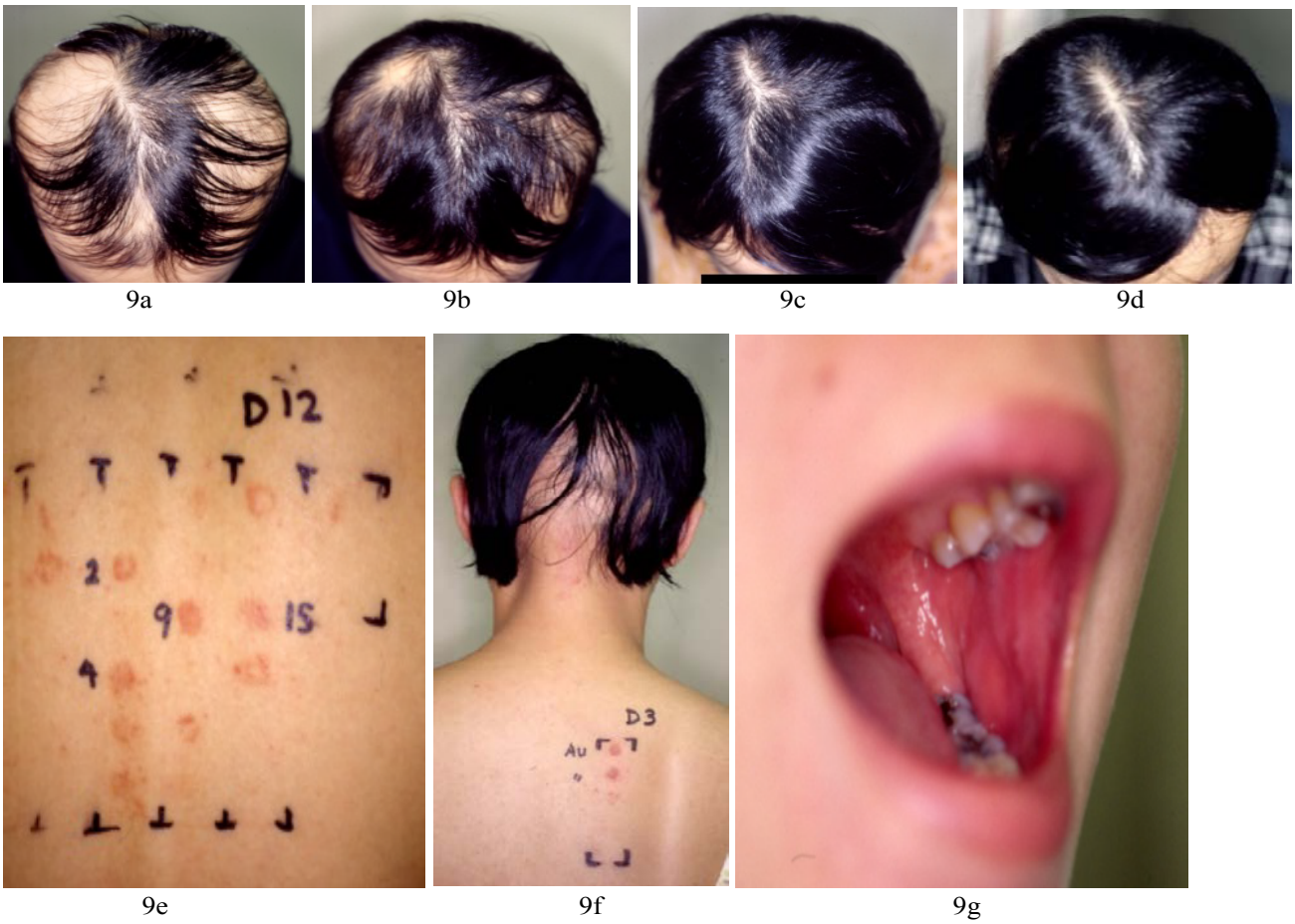

Figure 9: A case of metal hypersensitive alopecia areata.

Note: A 28-year-old woman started defluvium at the age of 6, and at 12 years of age, it developed to alopecia universalis. Antisymptomatic treatment by her doctor brought temporary cure by the age of 24. However, gradually alopecia areata multiplex spread on the whole scalp (9a) and became persistent. A patch test revealed she had multiple allergies to metals including Ni, Co, Hg, Au, Ir, Pd, Sn, Pt and Mo (9b). Confirmative patch tests to Au were positive (9c), and cross reactions of Ni, Co and Hg, Au were definite. Her 8 dental metals (9d) were analyzed to show the presence of 2 Hgs, 6 Aus, and 6 Pds. The biopsy of the alopecia and patch test positive reaction to $NiSO_4$ showed that main infiltrates in both the specimen turned out to have been CD4 positive T lymphocytes. ANA 40 times dilution (+). IgE 156 IU/ml. As all the dental alloys contained at least one metal allergen, the patient consented to remove all the metals to be replaced to ceramics. Hg-free type inoculation for flu has been injected almost every year. Hair regrowth at alopecia resion started after the elimination of metals, and one year later, the recovery was satisfactory (9e), and a follow up study 2 years later (9f) and 6 years later (9g) have shown no sign of relapse.

Table 5: Evidence that house dust mite allergy is the main causation of atopic dermatitis (AD) [32].

1.	Serum IgE level is usually higher with AD compared to other atopic diseases, such as pure bronchial asthma, pure allergic rhinitis and pure urticaria. The average serum IgE with the latter three is 330 IU/ml, but with these three complicate eczema of AD, the average serum IgE levels goes over 1,000 IU/ml to 6,000 - 7,000 IU/ml.
2.	77 - 87% of serum IgE in AD was due to Dps when the factors that raise IgE were counted, eliminating cross reactions to similar allergens, such as Dp and Df, Malassezia and Pityrosporum.
3.	Bruynzeel-Koomen discovered that IgE molecules present on dendric cells in the epidermis of AD react to airborne antigen and produce eczema. By this, type I allergy exerted by IgE is altered to type IV allergy of eczema.
4.	When three live mites were crushed on slightly convex plastic discs of 8 mm in diameter, they produced clear positive eczematous reactions with AD patients, regardless of the value of serum IgE and RAST results. The reactions were all negative (0/18) with Df on controls, and there was statistical significance between the positive rate of AD (10/45=22.2%). An important phenomenon was that one crushed live mite or dead dry mites never produced positive reactions. It meant that when the mite numbers /m2 is less than 50, the patient lose contact to HDM, to escape from mite allergy.
5.	Type IV allergy to HDM was discovered by Rawl in 1984 by experiment results that showed lymphocytes of AD reacted to mite allergen P1 at 50% of patients, while none of the controls reacted.
6.	α-acaridial, a terpene discovered from HDM, is a primary sensitizer and considered as a causation of Prurigo Besnier.
7.	When the mite fauna of AD patient's homes were investigated by the methylene blue agar (MBA) method, followed by an environmental improvement, severe intractable AD patients were cured completely at the rate of 70.6% (60/85) and the cure was maintained. Double blind tests have confirmed this fact.

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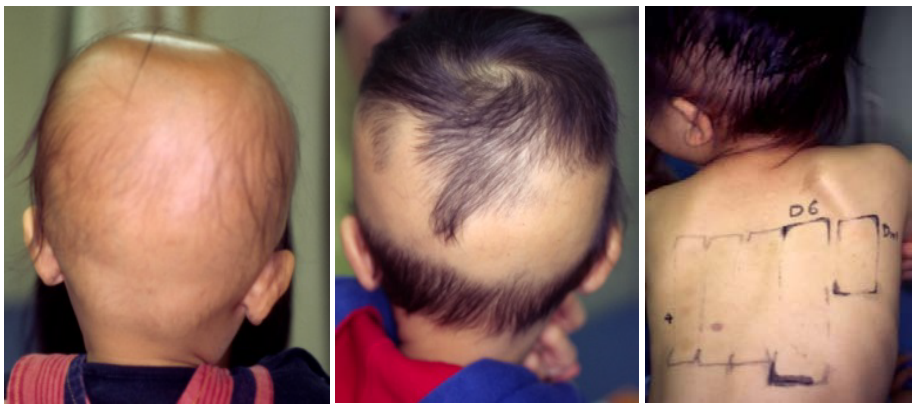
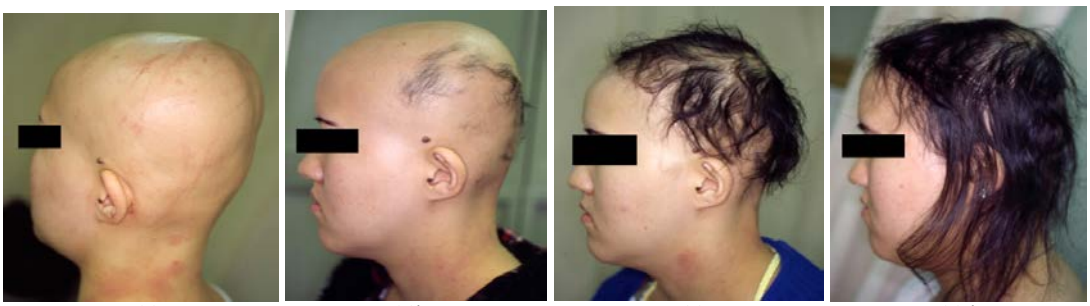


10a 10b 10c

Figure 10: A case of atopic alopecia.

Note: A one-year-old baby (male) suffered from atopic dermatitis (AD) since 6 months previously, and also alopecia universalis had developed. A patch test revealed he had type IV mite allergy so the mite fauna of his home was investigated, followed by the technique described in table 6 to reduce the mite numbers to less than 50 everywhere in his home. It meant his contact to HDM at 10 × 10 cm area became less than one mite thereafter, and herb lotion containing 2% salvia miltiorrhizae radix was applied, as the systemic usage of corticosteroid hormone is contra-indication because of growth inhibition [2]. This mite reduction and application of herb lotion was successful, as hair regrowth was noted remarkably and defluvium stopped 6 month later. There was no relapse after 6 months (10c) and a confirmative patch test still showed positive patch test reaction to HDM, however alopecia was no longer present by the elimination of HDM.



11a 11b 11c 11d

11e 11f

Figure 11: A case of atopic alopecia.

Note: A 20-year-old female had suffered from mild eczema of mainly flexor surfaces of the extremities since childhood. One year previously, alopecia started on the scalp, and developed to alopecia universalis (11a). Serum IgE level was 909 IU/ml, and RAST values were Dp 89 UA, Df 58 UA respectively. A patch test showed no allergy to metals, but positive reaction to Dermatophagoides mix® allergen. Serum ANA was 40 times dilution positive, and it was normal range for female. As the symptoms of alopecia were severe and as there was no evidence of allergen other than HDM, she was recommended to request investigation of mite fauna of her own house (11b). It was revealed that out of 11 specimen of the house dust collected, 6 specimen showed dermatophagoides from 459 to 192/m^2/20seconds aspiration by a 320 W cleaner. Environmental improvement was advised to dispose of mite-rich substances shown in red in fig.11c. A mite-free mattress was purchased and used every night, and owing to these procedures, her contact to HDM to which she was hypersensitive was considered to have decreased greatly. 3 months after that, short hair was noticed to grow on the scalp (11d), and the hair growth continued until a almost cured condition within 6 months (11e). There has been no relapse of alopecia during the 2 years of follow up (11f).

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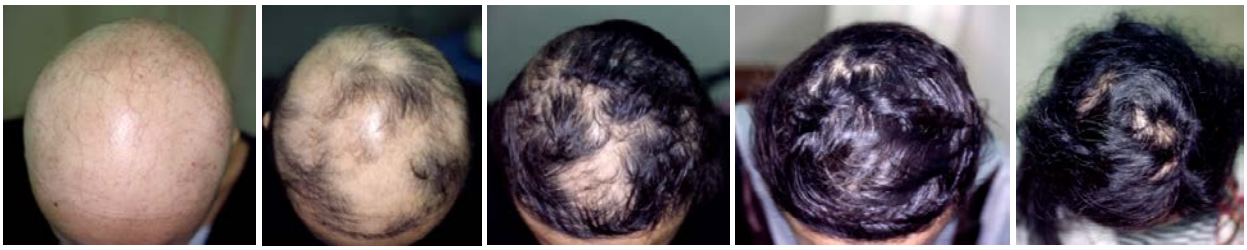
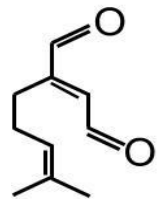


12a 12b 12c 12d 12e

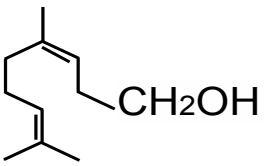
Figure 12: A case of atopic alopecia

Note: A 20-year-old woman started suffering severe defluvium from six months previously. Alopecia started from the right temporal area and soon developped to alopecia universalis (12a). Asthma bronchial and mild itchy xerotic eczema were present on her trunk and extremities. This atopic dermatitis had been present since she was a one-year-old. TPHA was (-), ANA was 80 times dilution positive. CBC, liverfunction test results were normal. Serum IgE was 2,700 IU/ml, RAST for Dp 404 UA, Df 346 UA, dog dandruff 6 UA. Patch test results: M-9 all negative. Dermatophagoides mix (+) at 72 hrs. She was diagnosed as atopic alopecia, and the only known positive allergen was HDM. She requested mite fauna investigation. Among 21 places in her home composed of 5 rooms. HD from 14 places many HDMs were found. The number of HDM ranged from 1,620 to 85, in 20 places the mite number was over 100, and at 5 places over 300, and at 3 places over 1,000/m^2. Besides HDM, a large amount of mite feces were found in her sleeping mat and cushion. These were soon all improved through introducing flooring all around the house, mite-free matts and pillows were purchased, mite rich teddy bears were disposed, vaccum cleaners were used on a weekly basis. Soon after this improvement, her hair started to grow (12b), and PSL pulse therapy at 10 mg a day for two months was stopped when an almost cured condition was obtained (12c). After that she used herb lotion to regrow hair [2], and after one year (12d) and four years (12e) there have been no relapse. At the point of 12e, her serum IgE had dropped to 1,320 IU/ml.



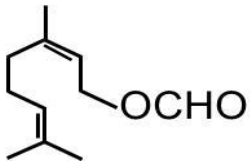
(1) α-acaridial

α -acaridial is a strong sensitizer that reacts positively for more than 2 weeks to 6 months, and at the same time is also a primary sensitizer. This is believed to be a causation of Prurigo Besnier of atopic dermatitis.



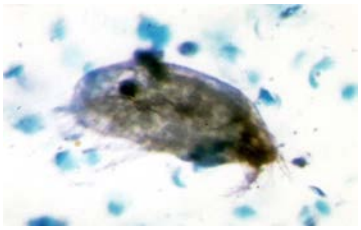
(2) Geraniol

Geraniol is a fragrance having the scent of roses. It is a common contact sensitizer present in soaps and various cosmetics. In the lipids of dermatophagoides mites, geraniol and geranial are present at 0.05% by gas chromatography.



(3) Geranial

Geranial is an aldehyde of geraniol. This acts similarly to geraniol as an allergen.



(4) Dermatophagoides found in the house dust of an atopic dermatitis patient's home (Meth ylene blue agar method). [32]

Figure 13: HDM and terpen allergens in HDMs.

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Table 6: Necessary mite fauna investigation and the methods of mite elimination in order to achieve less than 50/m^2 everywhere in the house for patients with severe intractable atopic alopecia.

1.	Serum IgE level with RAST on Dp and Df should be studied. When the results are normal, perform a patch test to HDM on Finn Chambers using Dermatophagoides mix® antigen (Chemotechnique Co, Sweden).
2.	Even when serum IgE level is normal or low, and the IgE RAST for Dps and Dfs is negative, such cases are not the so-called intrinsic AD, but the possibility of type IV allergy to HDM is high. It can be demonstrated by a patch test using the Dermatophagoides mix®. This patch test should has be performed for 2 days, and the reactions should be read on days 2, 3 and 7, because a late phase positive reaction is quite common.
3.	When type I or IV allergy to HDM is discovered, somebody (if possible, an astrologist) should visit the AD patient's home with a vacuum cleaner and small paper bags to be put in the duct, so that they can collect house dusts of the patient's home from 10 - 15 places for 1m2 for 20 seconds. Sleeping mats, pillows, bed mat, carpets, sofas, chairs, rags are important with which mite fauna should has be investigated.
4.	House dusts should measure with weight (x mg), and 50 mg of it is put into a petri dish, and then melted 0.01% methylene blue containing agar at 4 ml is poured into it. After it becomes solid at room temperature, counting the mites (y) in 50 mg of house dust at one place is possible. The actual number of house dust is xy/50/m2.
5.	Statistically, 90% of HDM are Dp or Df, to which the patients are hypersensitive towards.
6.	Start environmental improvement to decrease house dust mites to less than 50/m2 everywhere. If this has attained, the improvement of AD on skin and atopic alopecia could has be expected.
7.	If in some places the improvement has ignored, for example, by not to using mite-free mattress or mite-rich carpets and rags are not disposed, the improvement of severe AD or atopic alopecia is not to be expected.
8.	Flooring all the interior of the house has most recommended, along with the usage of mite-free sleeping mats. In cold climates, the introduction of heater flooring has recommended.

Table 7: The rate of satisfactory improvement of severe alopecia areata with which hair regrowth was noted over more than 70% of the scalp (Years 1996-2015).

Metal hypersensitive alopecia areata	
Patch test positive to metals	102/146 = 69.9%
Rate of improvement after elimination of metals from oral cavity and or pans and pots (Cure continued for 2 to 12 years for an average of 4 years, and 4 months)	37/49 = 75.5%
Atopic alopecia	
serum IgE > 250 IU/ml	29/64 = 45.3%
Rate of improvement after environmental improvement	14/24 = 58·3%
Alopecia presumably due to autoimmunity	
serum ANA positive (at 1:160 ~ 1:320 dilution)*	3/70 = 4.3%
Rate of improvement only through anti-symptomatic treatment	0/3 = 0.0%

Note: *Serum ANA positive at 1:80 dilutions or less turned out to be within normal female limit.

as a causation, but what exact component of human hair follicles produced autoimmunity has been obscure. After the new millennium, metal allergy was found in AA at 69.9%, and also the analysis of dental metals and cooking instruments followed by the elimination of allergenic metals with substitutes by ceramics showed the evidence of cure for a long period. Immune privilege (IP) of keratin is surely broken, when metals perorally taken, absorbed from intestine and carried to hair follicle keratin via blood stream make complete antigen of metal-combined keratin. Antisymptomatic treatment only produced severe alopecia again more than 50%, but the allergen control on metals could maintain the cured condition of AA at 75.5% in average for 4 years and 4 months.

Another type of AA has been called atopic alopecia, and most of the cases are not sensitized by metal, but they are sensitized by house dust mites (HDM). Type I and IV allergies to HDM exist. Severe types of atopic alopecia could be cured by the mite fauna investigation of the patient's homes by the MBA method, followed by an environmental improvement to reduce mite numbers to less than 50/m^2, because the patients could lose contact to HDM at less than 1 or 0 at 10×10 cm^2 everywhere. These cases regained hair at 58.3%, even though their previous symptoms were severe. When 6 years or more elapsed since the onset, and curing was found to be very difficult, because the biopsy of such cases revealed that hairfollicles were not present, leaving small debris fragments with surrounding fibrosis. AA should be examined for the allergens of metals and HDM, and should be treated by allergen control / allergen elimination before allergic reactions devastate precious hair follicles in wide areas.

References

1. Ioffreda, MD (2015) Alopecia areata, Lever's Histopathology of skin (11th Edtn) Wolters Kluwer, NY: 545-595.
2. Nakayama H, Chen KR (2017) Herb lotions to regrow Hair in patients with intractable alopecia areata Clin Med Invest 2: 1-7.
3. Koizumi M, Nakayama H. Ebihara T (1998) Laboratory test results and the effect of treatment in 106 cases of intractable alopecia areata. Jap J Dermatol 108: 1881-1891.
4. Gilhar A, Landau M, Assy B, Sharaginov R, Serafimovich MS, et al. (2002) Mediation of alopecia areata by cooperation between CD4+ and CD8+ T lymphocytes: transfer to human scalp explants on Prkdc (scid) mice. Arch Dermatol 138: 916-922.
5. Tobin DJ, Orentreich N, Fenton DA, Bystryn JC (1994) Antibodies to hair follicles in alopecia areata. J Invest Dermatol 102: 721-724.
6. Tobin DJ, Hann SK, Song MS, Bystryn JC (1997) Hair follicle structures targeted by antibodies in patients with alopecia areata. Arch Dermatol 133: 57-61.
7. McElwee KJ, Freyschmidt-Paul P, Hoffmann R, Kissling S, Hummel S, et al. (2005) Transfer of CD8(+) cells induces localized hair loss whereas CD4(+)/CD25(-) cells promote systemic alopecia areata and CD4(+)/CD25(+) cells blockade disease onset in the C3H/HeJ mouse model. J Invest Dermatol 124: 947-957.
8. Kern F, Hoffman WH, Hambrick GW Jr, Blizzard RM (1973) Alopecia areata, Immunologic studies and treatment with prednisone. Arch Dermatol 107: 407-412
9. Winter RJ, Kern F, Blizzard RM (1976) Predonisolone therapy for alopecia areata. Arch Dermatol 112: 1549-1552.
10. Michalowski R, Kuczyńska L (1978) Long-term intramuscular triamcinolon-acetonide therapy in alopecia areata totalis and universalis. Arch Dermatol Res 261: 73-76.

11. Kurosawa M, Nakagawa S, Mizuashi M, Sasaki Y, Kawamura M, et al. (2006) A comparison of the efficacy, relapse rate and side effects among three modalities of systemic corticosteroid therapy for alopecia areata. Dermatology 212: 361-365.
12. Nakayama H, Nogi N, Kasahara N, Matsuo S (1990) Allergen control. An indispensable treatment for allergic contact dermatitis. Dermatol Clin 8: 197-204.
13. Turjanmaa K (1997) Contact Urticaria from Latex Gloves, Contact Urticaria Syndrome. CRC Press, NY: 173-187
14. Nakayama H (2002) New aspects of metal allergy. Acta Dermatovenerol Croat 10: 207-219.
15. Finne KAJ, Goransson K, Winckler L (1982) Oral lichen planus and contact allergy to mercury. Int J Oral Surg 11, 236-239.
16. Stenman E, Bergman M (1989) Hypersensitivity reactions to dental materials in a referred group of patients. Scand J Dent Res 97: 76-83.
17. Nakayama H (1995) The role of house dust mite in atopic eczema, Practical Contact Dermatitis. Mc Grawhill, NY: 623-630
18. Seidenari S, Manzini BM, Danese P, Giannetti A (1992) Positive patch tests to whole mite culture and purified mite extracts in patients with atopic dermatitis, asthma, and rhinitis. Ann Allergy 69: 201-206.
19. Tanaka Y, Takenaka M, Matsunaga Y, Okada S, Anan S, et al.(1995) High affinity IgE receptor (Fc epsilon RI) expression on eosinophils infiltrating the lesions and mite patch tested sites in atopic dermatitis. Arch Dermatol Res 287: 712-717.
20. Ikeda T (1965) A new classification of alopecia areata. Dermatologica 131: 421-445.
21. Katsuoka K, Arai A, Kameyama K, Noguchi T, Nishiyama S (1992) Atopic alopecia areata, Hifubyo-Shinryo. Dermatosis Treat 14: 729-733.
22. Guo H, Cheng Y, Shapiro J, McElwee K (2012) The role of lymphocytes in the development and treatment of alopecia areata. Expert Rev Clin Immunol 11: 1335-1351.
23. Paus R, Bertolini M (2013) The role of hair follicle immune privilege collapse in alopecia areata: status and perspectives. J Investig Dermatol Symp Proc 16: s25-s27.
24. Shanon J (1965) Pseudo-atopic dermatitis. Contact dermatitis due to chrome sensitivity simulating atopic dermatitis. Dermatologica 131: 176-190.
25. Nakada T, Iijima M, Nakayama H, Maibach HI (1997) Rôle of ear piercing in metal allergic contact dermatitis. Contact Dermatitis 36: 233-236.
26. Fleischman P (1928) Zur Frage der Gefährlichkeit Kleinster Quecksilber Mengen. Dtsch Med Wochenscher: 304.
27. Kubo Y, Nonaka S, Yoshida H (1992) False positive reaction to patch testing with aqueous mercuric chloride in an aluminum Finn Chamber. Contact Dermatitis 26: 136-137.
28. Nakayama H (2001) The effect of long term administration of glycyrrhizin plus application of herbal lotion on intractable cases of alopecia areata, Nishi-Nichi Hifu (West Japan Derma) 63: 191-196.
29. Nakayama H (2004) Metal allergy, Hifu To Biyou (Skin and Cosmetic Treatment). 36: 124-132.
30. Nakayama H (2006) Dental Metal Allergy. J Environ Dermat 13: 37-65.
31. Nakayama H, Kumei A (2012) A new disease due to metal allergy –metal hypersensitive alopecia. Allergy no Rinsho (The Allergy in Practice) 432: 697-702.
32. Nakayama H, Kumei A, Chen KR, Takaoka M (2018) Mite Fauna Investiation Followed by Environmental Improvement Is Essenetial In Treating Intractable Atopic Dermatitis. Clin Med Invest 3: 1-13.

Author Affiliations

Top

Meguro Chen Dermatology Clinic, Tokyo, Japan